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ORIGINAL PAPER

Cultivation of mushrooms for production of food biofortified with lithium

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Abstract It has recently been suggested that food fortification with Li is worth serious consideration as a strategy to support psychiatric treatment and decrease violent behaviors in the general population. Therefore, the present study developed the cultivation of three commercially important mushroom species, *Ganoderma lucidum*, *Pleurotus eryngii* and *Pleurotus ostreatus*, on substrates enriched with Li (0.25–1.0 mM) in the form of acetate or carbonate. The growth of the mycelium colony, production of fruiting bodies and accumulation of Li were evaluated. Analysis of Li was performed using an optical emission spectrometry with excitation by inductively coupled plasma using an Agilent 5100 ICP-OES spectrometer. As found, Li_2CO_3 was a more bioavailable form although it had a greater adverse effect on mushroom growth. Substrate supplementation with CH_3COOLi resulted in lower or no growth retardation but decreased uptake of Li. The most promising results were obtained for *G. lucidum*, which accumulated up to 73.58 ± 10.87 (Li_2CO_3) and 25.59 ± 9.98 (CH_3COOLi) mg Li kg^{-1} dry mass. Given the popularity of the investigated mushroom species in various cultures as food or alternative medicines, their Li-biofortified forms could potentially find social acceptance. The concentrations of Li accumulated in fruiting bodies were not high enough for application in psychiatric treatments but could potentially support the daily intake of Li for behavior modification or health beneficiary purposes. Further studies are necessary to fully investigate the safety implications of Li-enriched mushrooms for humans.

Keywords Lithium · Biofortification · *Ganoderma lucidum* · *Pleurotus eryngii* · *Pleurotus ostreatus*

Introduction

Mood disorders, including bipolar disorder, represent an important category of mental illnesses, whose prevalence is generally increasing in developed countries. Over the years, a number of psychopharmacological agents have been introduced, with lithium (Li) cation being one of the most promising and effective, primarily in the recovery of bipolar affective disorder [1]. However, its potential therapeutic application spectra are much wider with evidence supporting its use in the treatment of unipolar depression [2], acute mania and its prophylactic [3, 4], or reduction in suicidal and aggressiveness rates in affective disorders [5, 6] and conduct disorder [7]. It is also speculated whether Li could be used in treating neurodegenerative disorders including Alzheimer's disease and, importantly, its prevention [8]. Apart from a purely applied medical use, some authors have suggested that nutritional intake of Li could be potentially beneficial for mood stabilization and may lead to a decrease in aggressive behavior in the general population [9–11].

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Unlike many traditional psychopharmacological compounds, Li does not bind to a cellular receptor but modifies the intracellular second messenger system. Its main postulated mechanisms of action are based on effects excreted on inositol monophosphatase (IMPase) within the phosphatidylinositol (PI) signaling pathway and the protein kinase glycogen synthase kinase 3β (GSK-3β) [12]. Calcium carbonate taken orally as pills is the most often applied form [13]. However, Li may also be supplied in relatively low doses with diet, particularly through consumption of grains and vegetables, and also in some areas with drinking water [14]. Interestingly, decreased levels of dietary intake of Li have been potentially linked to the prevalence of manic-depressive psychosis [15] and rates of suicides, homicides, or even the arrest rates for drug use and other crimes [16]. Altogether, this supports the hypothesis that Li consumption with food may have prophylactic value in the primary prevention of mood disorder [17]. However, most food products are poor in Li [14], while the use of Li-containing pharmaceuticals is likely to be socially linked with serious mental illness [10].

Information on natural Li content in mushrooms is scarce. Its mean concentration reported for wild-growing mushrooms collected from different locations in Hungary and Italy amounted only to 0.19 and 0.25 mg kg^{-1} dry weight, respectively [18, 19], while in cultivated *Pleurotus* mushrooms, Li content was found to be below detection limit [20]. Recently, however, the concept of mushrooms enriched in various elements such as selenium, zinc or copper for use as functional foods has been developed [21–23]. Mushrooms are a potentially rich target of such a biofortification strategy owing to their ability to accumulate various elements present in the overgrown substrates [24]. They also represent traditional natural products used widely in various cuisines [25], and some species are well recognized for their potential medicinal use [26]. Moreover, commercial cultivation of mushrooms can be made cost- and time-effective [27]. And Li fortification of food has recently been highlighted as worth serious consideration [9]. Li-enriched mushrooms may represent an interesting and more socially acceptable alternative in dietary supplementation of this element for various health beneficiary purposes. Nevertheless, to date the bioenrichment of mushrooms with Li has largely been ignored—only one study assessed the ability of *P. ostreatus* to accumulate Li added to the cultivation substrate in the form of LiCl [28]. As reported, the supplementation significantly increased Li concentrations in fruiting bodies (reaching maximally over 150 mg kg^{-1}) and did not alter crude protein content.

The aim of the present study was to evaluate the feasibility of mushroom species: *G. lucidum* (known as "Chinese Lingzhi"), *P. eryngii* and *P. ostreatus* (known as "king oyster" and "oyster" mushroom, respectively) for bioenrichment with Li in the form of carbonate and acetate. All three mushrooms are commercially important species, valued for their nutritional properties, with various medicinal uses reported in in vitro and in vivo studies [29, 30]. Our study highlights that they may additionally represent promising carriers of dietary Li.

Materials and methods

Experimental design

The substrate for *P. ostreatus* was prepared from a mixture of beech and alder sawdust (1:1 vol.), additionally supplemented with wheat bran in the amount of 20%, wheat straw chaw 10%, corn flour 5%, soybean meal 3%, chalk 1% and gypsum 1% in relation to the substrate weight. For *P. eryngii* and *G. lucidum*, a mixture of beech and alder sawdust was also used, but the following supplements were added: wheat bran 20%, corn flour 5%, soybean meal 3%, sucrose 1% and gypsum 1%. The mixtures were moistened to 45% of water content using distilled water, placed in polypropylene bags and sterilized at 121 °C for 1 h. Li was added to the substrate in the form of solutions prepared from Li_2CO_3 or CH_3COOLi (Sigma-Aldrich) in concentrations of 0.25, 0.5, 0.75 and 1.0 mM. The moisture of the substrates after Li addition was 60%. The substrates were mixed with grain spawn of tested mushroom species (5% of substrate weight) and placed in 17 × 25 cm polypropylene foil bags with a filter (*P. ostreatus* and *G. lucidum*) or in 1-L polypropylene bottles with a cellulose filter type 338 (Munktell, Bärenstein, Germany) with a basic weight of 84 g/m^2 and typical retention of 12–15 µm (*P. eryngii*).

Sterile Petri dishes for mycelium growth testing were used. The dishes were filled with the examined substrates after which three grains of mushroom spawn were placed in their central part. Incubation was conducted at 25 °C for 9 days. After that time, the diameter of the mycelium colony was noted.

The incubation in bags and bottles was conducted at 25 °C and 80–85% relative humidity until the substrate became completely covered with mycelium. Next, the bottles with removed covers and bags with the top part of the foil cut off were placed in a cultivation chamber. For fructification, humidity was maintained at 85–90% and temperature at 16 ± 1 °C for *P. ostreatus* and *P. eryngii* and at 25 ± 1 °C for *G. lucidum*. The cultivation chamber was illuminated with fluorescent light of 500 lx intensity for 12 h a day and aerated to maintain CO_2 concentration below 1000 ppm. Fruiting bodies of *P. eryngii* and *P. ostreatus* were harvested successively as they matured. Yield included fruiting bodies with stipes from one flush of yielding for *P. eryngii* and two flushes for *P. ostreatus*.

Fruiting bodies of *G. lucidum* were harvested at once 45 days after inoculation.

Mushroom fruiting bodies were dried in an electric drier SLW 53 STD (Pol-Eko, Wodzisław Śląski, Poland) at 50 °C for 48 h, weighted and ground for 0.5 min in a Cutting Boll Mill 200 (Retsch GmbH, Haan, Germany). The powdered samples were treated in the extraction. The method described above was similar to that presented in the author's previous studies [21].

Instrument

An optical emission spectrometer with excitation by inductively coupled plasma Agilent 5100 ICP-OES (Agilent, USA) was used in radial plasma observation mode (wavelength 670.783 nm, radio frequency (RF) power 1.2 kW, nebulizer gas flow 0.7 L min^{-1}, auxiliary gas flow 1.0 L min^{-1}, plasma gas flow 12.0 L min^{-1}, viewing height 8 mm, signal accusation time 5 s for three replicates). The commercial analytical standard (Romil, England) was used for analysis. The detection limits were determined on the level of 0.01 mg kg^{-1} dry weight (DW as three-sigma criteria). The uncertainty for total analytical procedure (including sample preparation) was at the level of 20%. Results recovery of standard addition (used due to a lack of certified standard materials for phosphoric acid extraction) was 80–120%.

Procedure

Mushrooms were dried at 50 ± 2 °C for 24 h and at 80 ± 2 °C for 8 h in an electric oven (SLW 53 STD, Pol-Eko, Wodzisław Śląski, Poland) to dry matter and then ground in a laboratory Cutting Boll Mill PM 200 (Retsch GmbH, Haan, Germany). Accurately weighed 0.300 ± 0.001 g of a dry sample of mushroom was ultrasonically extracted by phosphoric acid 1 mol L^{-1} solution (Honeywell, USA). After extraction, samples were filtered and diluted with water to a final volume of 15.0 mL. Each of the samples was analyzed in triplicate using the whole sample preparation procedure.

Statistical analysis

The results were analyzed using STATISTICA 12.0 software (StatSoft, USA). One-way analysis of variance (ANOVA) followed by the post hoc Tukey's HSD test was applied to investigate the differences in Li accumulation and mushroom growth between the studied species. Correlations between Li content in fruiting bodies and their biomass were assessed with the Pearson correlation coefficient. $P < 0.05$ was considered as statistically significant.

Results

The effect of Li on the mycelium colony

The addition of Li_2CO_3 and CH_3COOLi resulted in a distinctively different response of mycelium growth (Fig. 1). Higher levels of Li_2CO_3 (0.75 and 1.0 mM for *P. eryngii* and *G. lucidum*, and ≥0.5 mM for *P. ostreatus*) significantly altered the mycelium colony growth (Fig. 1). In the presence of all concentrations of CH_3COOLi, mycelium of all three species developed intensively.

The effect of Li on fruiting body morphology and biomass

The characteristics of fruiting bodies obtained from Li-enriched cultivation are collectively presented in Fig. 2. Most cultivation models did not induce any visible macroscopic alterations. *P. eryngii* did not grow on substrates supplemented initially with 0.75 and 1 mM of Li_2CO_3, whereas fruiting bodies of *G. lucidum* were clearly deformed and lower in the presence of 1 mM of Li_2CO_3 (Fig. 2).

The biomass of the collected fruit bodies depended more on mushroom species than on the form of Li used for supplementation (Fig. 3). Generally, the greatest biomass was produced by *P. eryngii* grown with Li_2CO_3 and CH_3COOLi (mean for all concentrations was 96.0 ± 1.2 and 93.7 ± 5.0 g, respectively), while the lowest biomass was observed for *P. ostreatus* collected from the second flush of yielding (37.6 ± 7.6 and 41.5 ± 7.3 g, respectively). Biomass of *G. lucidum* fruiting bodies, in turn, was generally comparable over different CH_3COOLi concentrations and significantly affected by the highest level of Li_2CO_3 employed in this study. Similarly, CH_3COOLi did not induce significant changes in the biomass of *P. ostreatus* from the first flush of yielding, contrary to Li_2CO_3 which decreased mushroom biomass at the greatest substrate concentrations (0.75 and 1 mM).

Efficiency of lithium accumulation in mushroom species

The form of Li used in the experiment was crucial in its uptake and accumulation in mushroom fruiting bodies (Fig. 4). Generally, the accumulated content increased over the initial Li concentration. In most cases, a greater mean content of Li was noted when substrates were supplemented with Li_2CO_3 than CH_3COOLi. It should, however, be noted that *P. eryngii* did not grow at higher Li_2CO_3 concentrations. The greatest mean content of Li was found for *G. lucidum*, exceeding 70 mg kg^{-1} dm after the substrate was enriched with 1 mM of Li as Li_2CO_3 and 25 mg kg^{-1} dm following the substrate supplementation with 1 mM of

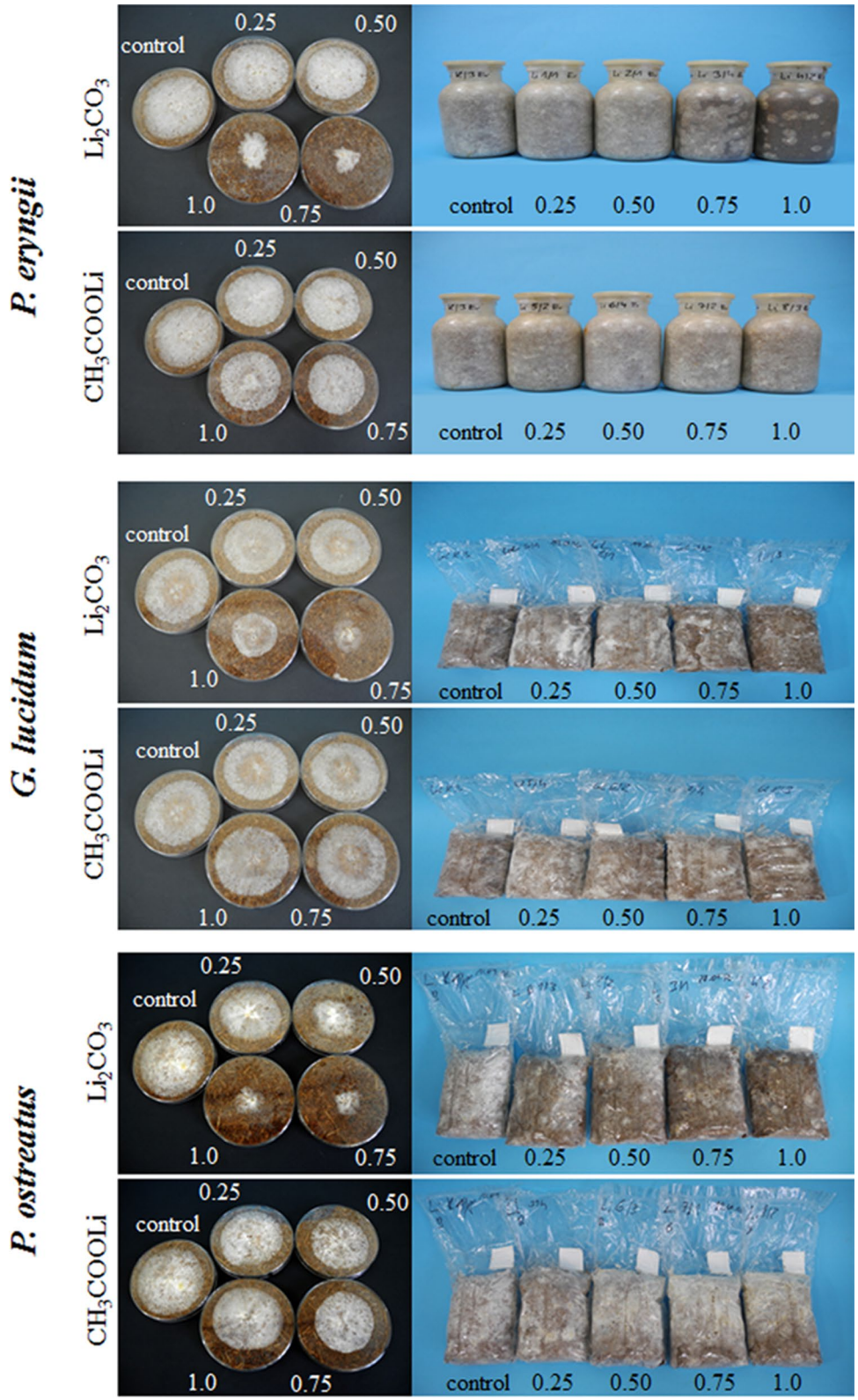

Fig. 1 Characteristics of mycelium colony of the studied mushroom species

Li in the form of CH_3COOLi. The maximum accumulation for *P. ostreatus* first flush was 12.0 mg kg^{-1} (Li_2CO_3) and 8.3 mg kg^{-1} (CH_3COOLi) and *P. ostreatus* second flush 16.5 mg kg^{-1} (Li_2CO_3) and 5.3 mg kg^{-1} (CH_3COOLi), and for *P. eryngii*, it amounted to 10.9 mg kg^{-1} (Li_2CO_3) and 15.1 mg kg^{-1} (CH_3COOLi).

There was a significant negative correlation between Li concentrations in fruiting bodies of *G. lucidum*, *P.*

Fig. 2 Morphology of mushroom species growing on substrate enriched with lithium carbonate and lithium acetate

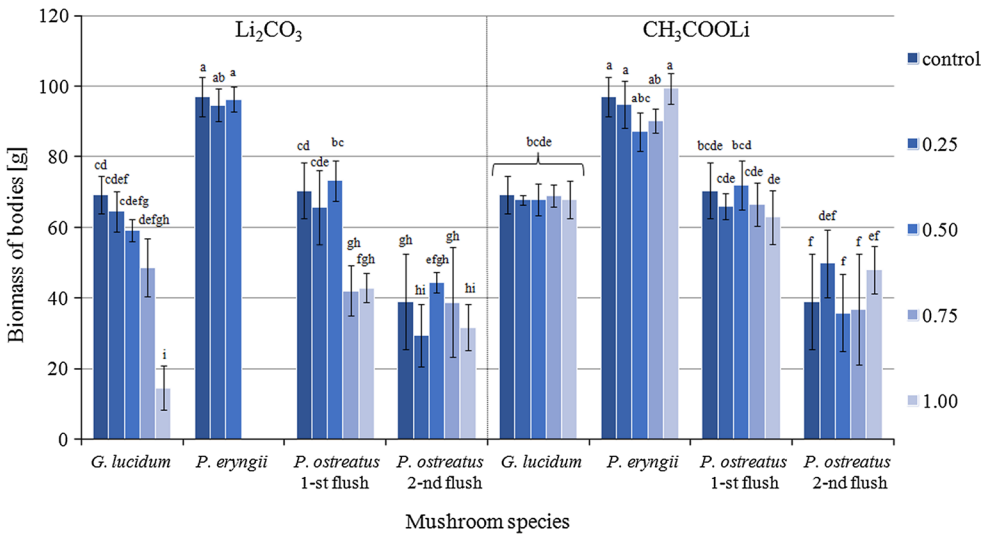

Fig. 3 Biomass (g) of mushroom species

eryngii and *P. ostreatus* first flush of yielding in the presence of Li_2CO_3, and the biomass of their fruiting bodies ($r = -0.98$, $r = -0.76$ and $r = -0.93$, respectively; $p < 0.05$). No statistically significant correlations were found between these two parameters when mushrooms were grown in the presence of CH_3COOLi and when *P. ostreatus* second flush of yielding was cultivated with substrates supplemented with Li_2CO_3 ($p > 0.05$ in all cases).

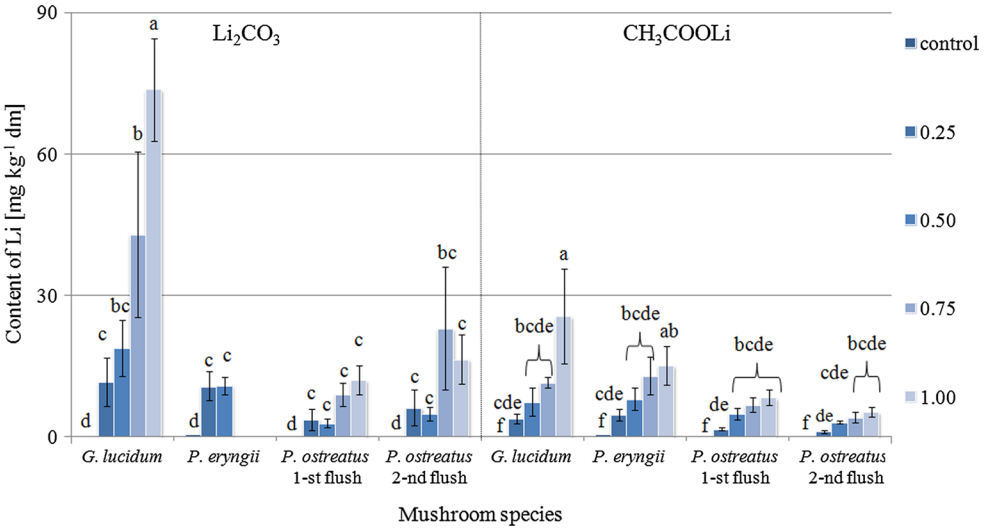

Fig. 4 Content of Li (mg kg^{-1} dry matter) in fruit bodies of mushroom species

Discussion and conclusions

The bioenrichment of mushrooms during their cultivation process is becoming increasingly studied as a promising strategy to produce functional foods [22, 23, 31]. It has been suggested that nutritional intake of Li may be beneficial for health, particularly in the prevention or amelioration of neurological and psychiatric alteration [32, 33]. The present study demonstrates that in fact, some mushrooms species may easily uptake Li from the overgrown substrate and efficiently accumulate it in their fruiting bodies without a significant alteration of their growth and morphology.

Potential commercial application of Li-enriched mushrooms as a nutraceutical would require their cultivation to be cost-effective and efficient as regards produced biomass. An artificially increased content of various elements in cultivation substrate may largely affect the growth and appearance of mushrooms and result in increased cultivation expenses as well as a decrease in the attractiveness of the final product for potential consumers and a lower market value [22, 34]. As demonstrated, the cultivated species were generally more resistant to Li in the form of acetate and developed a greater mycelium colony and subsequently larger biomass of fruiting bodies. This is in line with results obtained by Nunes et al. [35] who compared the growth of various white-rot fungi on potato dextrose agar supplemented with different forms of Li: acetate, chloride, hydroxide, sulfate and carbonate. The latter was found to be the most toxic; in its presence, no mycelium growth was observed for most of the investigated species (including *P. eryngii*). It should be highlighted that all Li compounds employed by Nunes et al. [35] decreased mushroom growth several-fold (except for *P. djamor*) compared to the control. This largely discourages the employment of non-composted substrates in enrichment of mushrooms with Li as the bioavailability of this element may be too high and lead to toxic effects. Previous investigations by de Assunção et al. [28] indicated that *P. ostreatus* may be successfully cultivated on coffee husk substrate supplemented with Li chloride. Our study adds further evidence that solid substrates with CH_3COOLi and Li_2CO_3 can also be used in bioenrichment of fruiting bodies.

Particularly promising results of the present study were obtained for *G. lucidum*. This species grew well on substrates supplemented with every concentration of CH_3COOLi, and in this case, maximal accumulation in fruiting bodies exceeded 25 mg kg^{-1} dry matter (DM). Although higher concentrations of Li_2CO_3, 0.75 and 1.0 mM, significantly decreased the biomass, the Li accumulation exceeded 40 and 60 mg kg^{-1} dry matter, respectively. The commercial application of Li-enriched *G. lucidum* may be additionally supported for the medicinal properties of this species, which have long been acknowledged [29, 36–38]. Considering that the market for *G. lucidum* is already worth over 2.5 billion US dollars [39], the commercial introduction of its Li-enriched form should not be troublesome. The safety of such a product should be first evaluated, preferably using both in vitro and in vivo models; its target group of potential consumers should be then clearly defined, presumably on the bases of randomized trials conducted on various populations.

The use of Li in the treatment of psychiatric disorders requires relatively high daily doses taken orally. These may even rise to as much as 600–1200 mg of Li_2CO_3 taken daily in divided doses, which equates to 113–226 mg of elemental Li [40]. Our study demonstrated that a single consumption of a meal containing 100 g of dried *G. lucidum*, *P. ostreatus* first flush, *P. ostreatus* second flush and

P. eryngii would constitute 7.4, 1.2, 1.6 and 1.9 mg of Li intake if substrates were fortified with 1 mM of Li_2CO_3 (or 0.5 mM in case of *P. eryngii*). To compare, consumption of the same amount of mushrooms grown on substrates supplemented with 1 mM of CH_3COOLi would equal a Li intake of 2.6 mg (*G. lucidum*), 0.8 mg (*P. ostreatus* first flush), 0.5 mg (*P. ostreatus* second flush) and 1.5 mg (*P. eryngii*). These calculations, however, do not include the partial loss, which may occur during mushroom processing, e.g., washing or cooking [25, 41]. Moreover, they do not consider the absorption kinetics in the gastrointestinal tract, although in vitro bioavailability of Li from mushrooms was reported to be very high, far surpassing that of the pharmaceutical drug containing Li_2CO_3 [28]. Altogether, it is more likely that Li-enriched mushrooms such as *G. lucidum*, *P. ostreatus* and *P. eryngii* may find a practical application in prophylactics of mood alterations rather than in psychiatric treatment. Importantly, moderately increased Li consumption may also be beneficial in stabilizing the mood of former alcoholics and drug users [32, 42]. Such food products could ensure an adequate dietary intake of Li for the purpose of decreasing the frequency of aggression and violence, as supported by observations that suicides, anxiety and homicides may be linked to low serum Li levels [43–45]. To maintain its physiological levels, the provisional recommended dietary allowance for Li in adults has been proposed at the level of 1 mg for a 70-kg adult, although tenfold higher doses were not reported to induce any adverse health effects [14]. To meet the nutritional demand for Li, some authors have recently suggested that cereal grain products be fortified with Li, or Li be added to dietary supplements [9]. Mushrooms may be an interesting or even superior option in this regard if one considers their popularity in different cuisines, their traditional use in various cultures for the maintenance of health and disease prevention and their social acceptance as foodstuffs [26]. All three species investigated in our study could serve as a source of moderately increased dietary Li at doses far below those reported to be toxic for humans [14]. On the other hand, the present study demonstrated relatively high variations of Li content in mushroom fruiting bodies as presented by SD values for each Li concentration, which may be a challenge in standardizing the Li levels in final food products obtained from such mushrooms. Further biomedical investigations, including experimental in vitro and in vivo models, are necessary to evaluate the medical potential of Li-enriched mushrooms.

In summary, the present study evaluated whether three commercially important mushroom species may be used in Li biofortification in order to produce Li-enriched fruiting bodies. Apart from investigating the Li accumulation, its effect on the mycelium colony and the biomass of fruiting bodies was also assessed. The most promising effects were obtained for *G. lucidum*, both in terms of growth and in terms of Li accumulation. The adoption of this species may be particularly interesting in increasing the dietary intakes of Li for mood modulation purposes, given its already established medicinal status. Mushrooms biofortified with Li may find their use in decreasing rates of aggressive behaviors—a hypothesis yet to be tested in randomized control trials preceded by safety evaluations.

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Compliance with ethical standards

Conflict of interest None of authors have a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Compliance with ethics requirements This article doe not contain any studies with human or animal subjects.

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